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THE UNITED STATES OF AMERICA

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February 07, 2005

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APPLICATION NUMBER: 60/535,908

FILING DATE: *January 12, 2004*

RELATED PCT APPLICATION NUMBER: *PCT/US05/00884*



Certified by

Don W. Dudas

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Provisional Application Cover Sheet

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This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

Docket Number: Q3399		Type a plus sign (+) inside this box		+
Inventor(s)/Applicant(s)				
Last Name	First Name	Middle Initial	Residence (City and either State or Foreign Country)	
Siegel Winey	Steven Karen		Berwyn, PA Philadelphia, PA	
Title of the Invention (280 Characters Maximum)				
A Long-Term Biodegradable Formulation for Risperidone and 9-oh-risperidone				
Correspondence Address				
University of Pennsylvania Center For Technology Transfer 3160 Chestnut Street Suite 200				
City: Philadelphia	State: Pennsylvania	Zip Code: 19104 - 6283	Country: US	
Enclosed Application Parts: (check all that apply)				
[X] Specification Number of pages: 16 [] Small Entity Statement				
[] Drawing(s) Number of sheets: [] Other (specify)				
Method of Payment (check one)				
[] Our Check No. _____ is enclosed to cover the Provisional filing fees. A duplicate copy of this sheet is enclosed.			Provisional Filing Fee Amount (\$)	\$ 80.00
[X] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 13-2489. A duplicate copy of this sheet is enclosed.				
[] Payment by credit card. Form PTO-2028 is attached.				

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

[] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Signature:

Typed or Printed Name: Steven Siegel

Date:

11/9/04

[] Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

22154 U.S. PTO
60/535908

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PROVISIONAL APPLICATION SUBMISSION TO USPTO – CONTENTS PAGE

Penn Docket Number : Q3399
First-named Inventor : Siegel
Submission Date : 1/12/04
Prepared by : Matt Thomas

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4-16	Risperidone Figures and Charts

Total Number of Pages : 16

Siegel, S. J. et. al. Risperidone and 9-OH Risperidone

Brief Summary

We have devised a long-term delivery formulation for the antipsychotic agent risperidone and its active metabolite 9-oh-Risperidone. Risperidone is currently in use for the treatment schizophrenia, bipolar disorder, Alzheimer's Disease, psychotic depression, and other mental conditions that cause confusion, disorganization and psychosis. The current formulation would allow for incorporation of both risperidone and 9-oh-risperidone into multiple delivery platforms including:

1. Surgically implantable formulation: this method would be best suited for the treatment of chronic conditions listed above.
2. Incorporation into nanoparticles for stealth long-term delivery through the GI tract. As PLGA loaded nanoparticles are delivered across the intestinal mucosa, active drug would evade first pass metabolism. Additionally, this method could deliver antipsychotic activity for one-week interval.
3. The use of 9-oh-risperidone is included since this molecule has a hydroxyl functional group that allows for ester bond formation, and creation of pro-drug polymers that will deliver improved controlled release as compared to physical mixtures.

Stage of development

We have tested multiple compounds in PLGA delivery systems in vitro. These studies indicate that every drug results in a different pattern of release. Risperidone and 9-oh risperidone result in a highly stable drug-polymer matrix with kinetics that approach steady state over the delivery interval, even with a polymer (50:50 PLGA) that traditionally yields a high degree of drug dumping after an initial lag. Additionally, we are able to make nanoparticles with PLGA and incorporate drugs into these particles for oral delivery systems.

Applications/Commercial use

The commercial application of this technology is related to treatment of schizophrenia, bipolar disorder, Alzheimer's Disease, psychotic depression, and other mental conditions that cause confusion, disorganization and psychosis.

Closest know similar technology

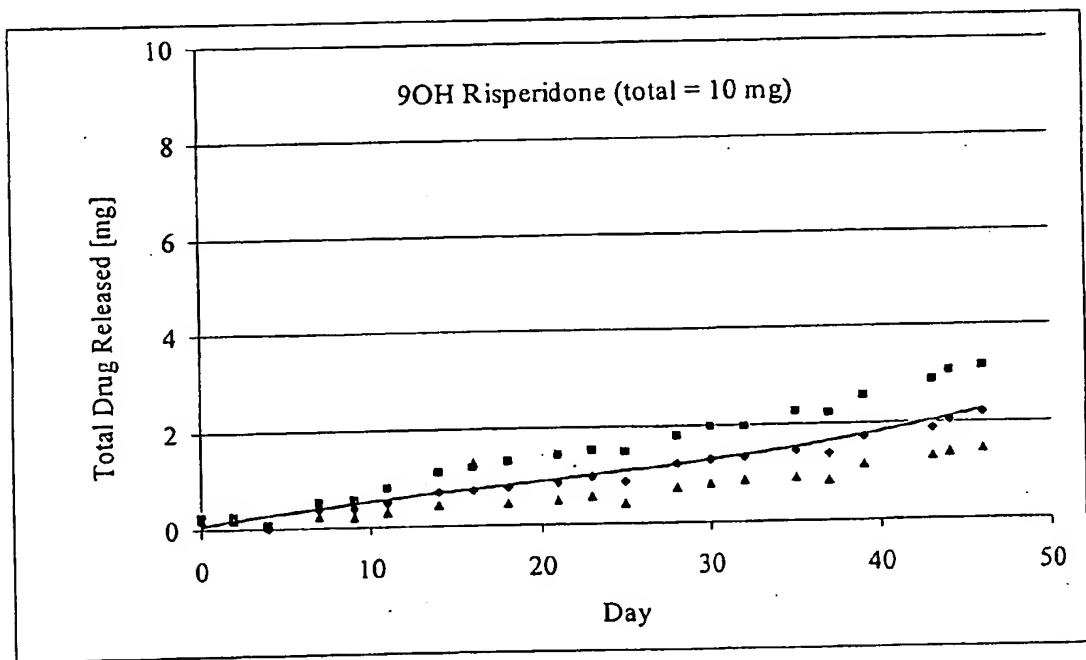
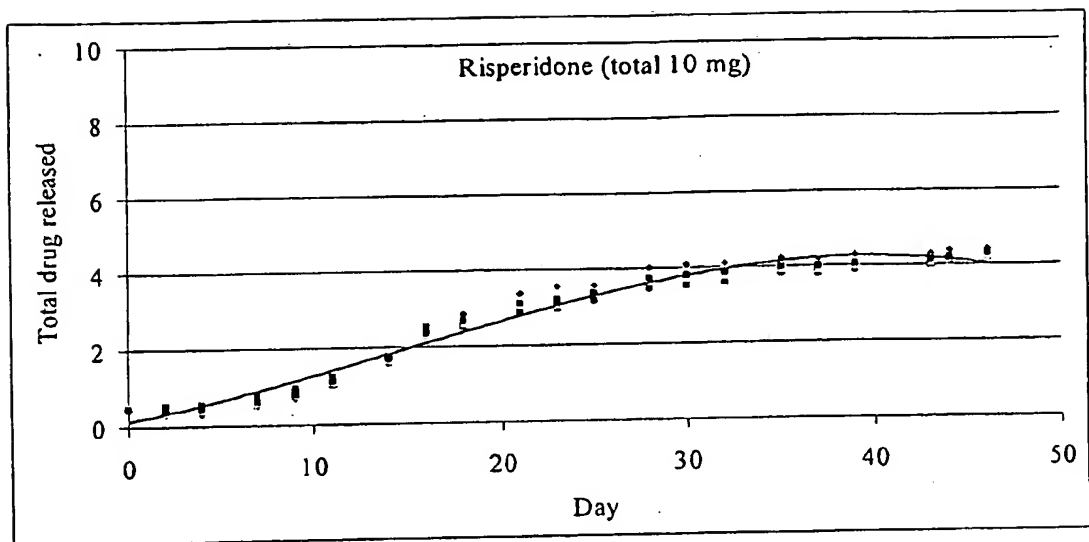
Current formulations of risperidone include daily oral formulations and biweekly PLGA based microspheres (Risperidone Consta). There are no pro-drug polymers utilizing 9-oh risperidone in use, or that we are aware of in development.

Differences / advantages

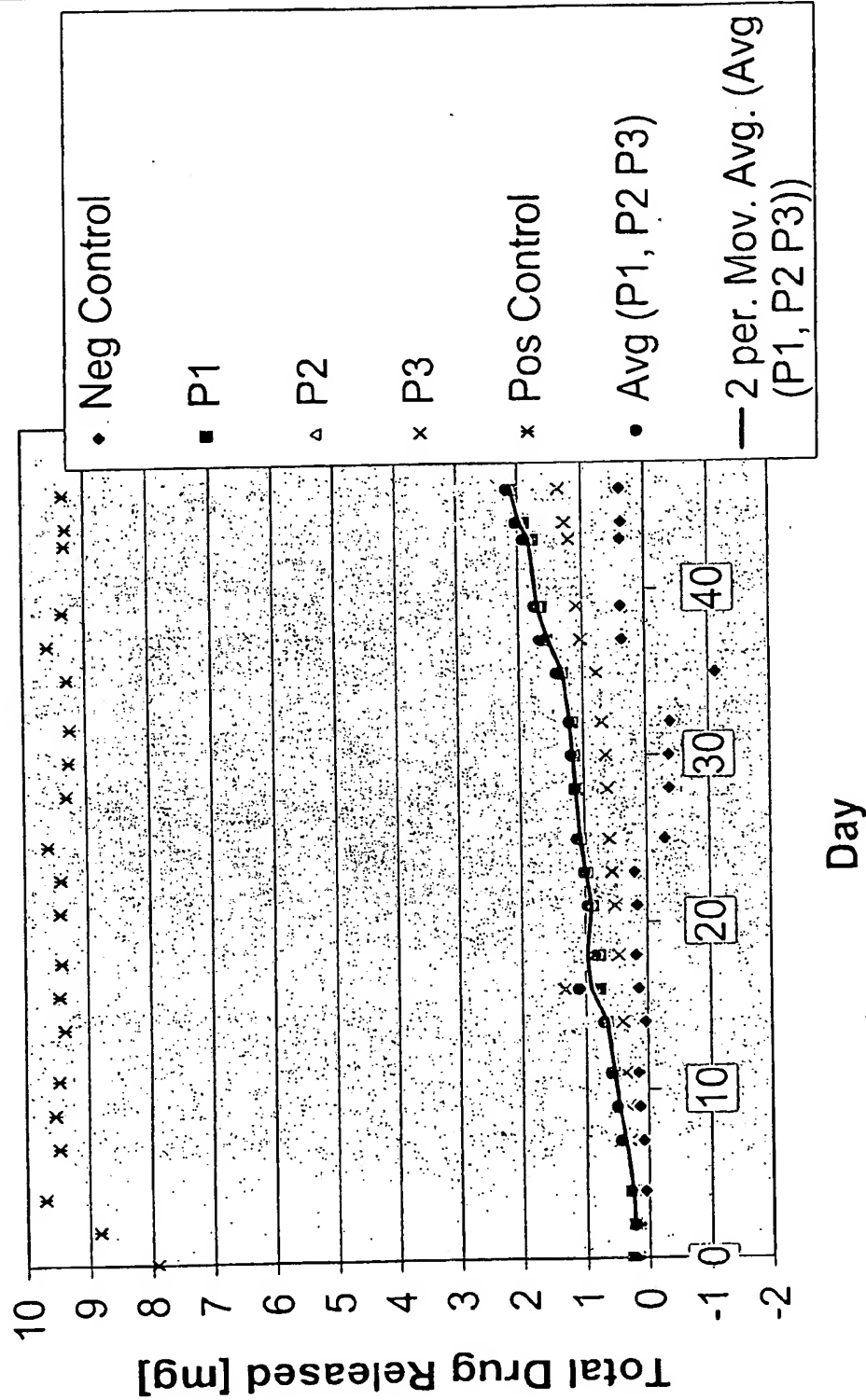
The major advantages to a long-term polymer based delivery system for this drug include:

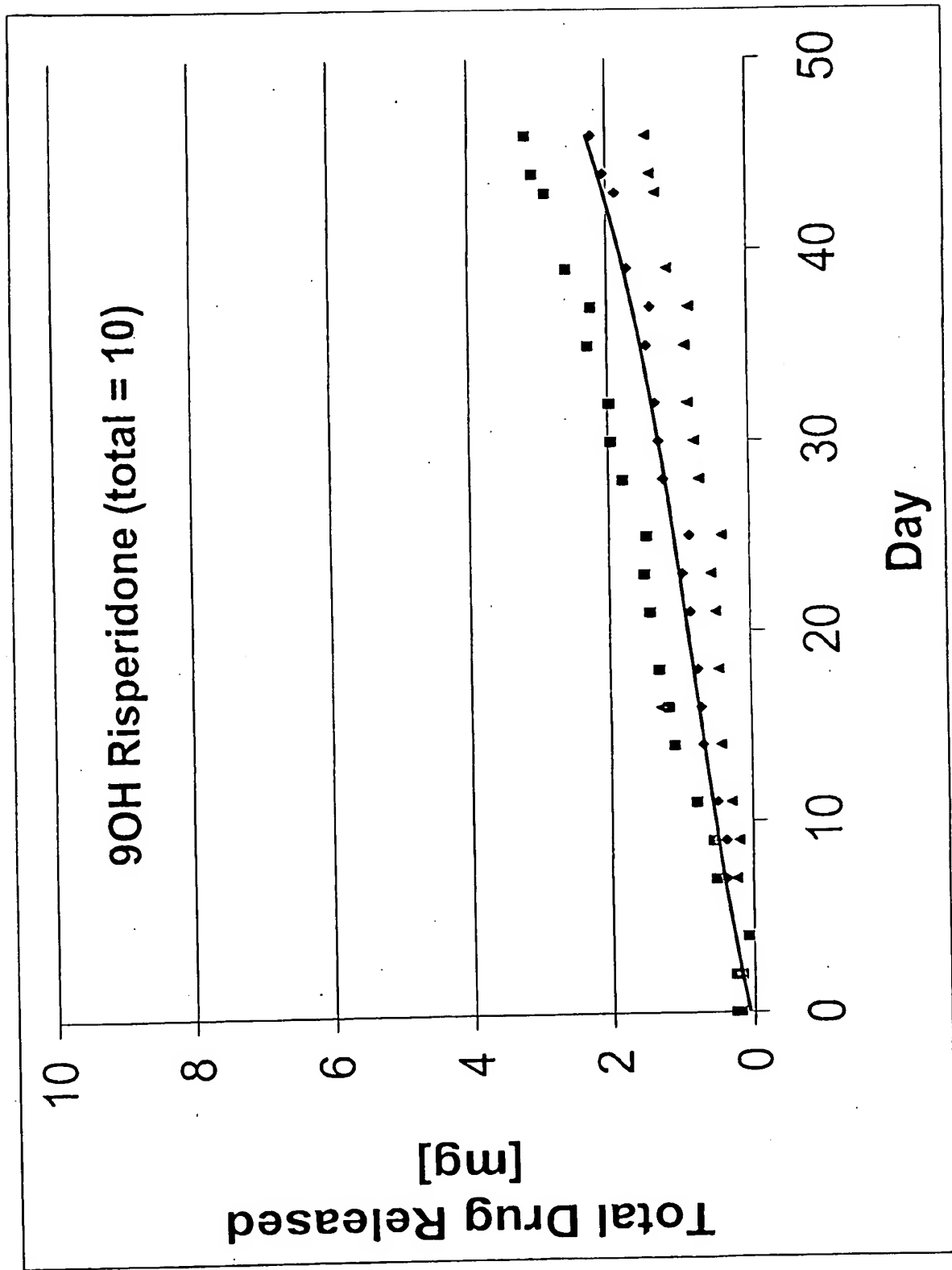
- Steady state delivery over weeks to months, avoiding peaks and troughs from oral dosing

- Lower dosing through avoidance of first pass metabolism resulting in less systemic toxicity.
- Greater ease of administration with resulting in improved adherence as compared to current oral medications.
- Long term implants t offer a degree of treatment adherence (annual) and resulting improvement that is not currently available in any psychiatric medication.



20% 85:15 90H



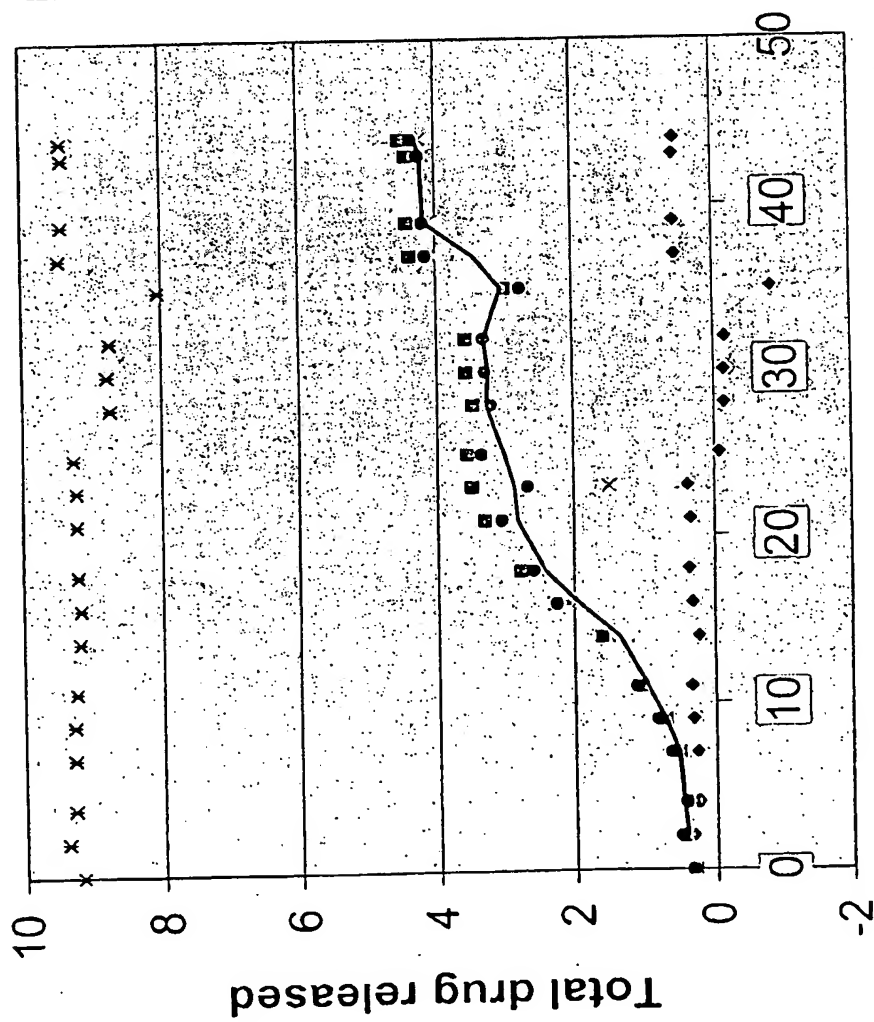


ABSORBANCE Day	Neg Control ABS	P1 ABS	P2 ABS	P3 ABS	Pos Control ABS	ABSORBANCE Day	Pos Control ABS	Pos Control Correction Coefficient	P1C ABS	P2C ABS	P3C ABS
0	0	0	0.004	0.004	0.001	0	0				
2	-0.001	0.002	0.004	0.004	0	2	0.014	-0.009	-0.005	-0.012	
4	-0.005	0.005	0.009	0.009	0	4	0.003	0.010	0.017	0.003	
7	-0.005	0.013	0.02	0.02	0.005	7	0.006	0.010	0.019	0.001	
8	-0.002	0.016	0.025	0.025	0.007	9	0.003	0.016	0.031	0.006	
11	-0.001	0.019	0.034	0.034	0.009	11	-0.002	0.026	0.046	0.013	
14	-0.007	0.024	0.044	0.044	0.011	14	0.002	0.027	0.050	0.035	
16	-0.002	0.029	0.052	0.052	0.057	16	0.000	0.029	0.056	0.016	
18	0	0.029	0.056	0.056	0.014	18	0.001	0.034	0.062	0.016	
21	-0.001	0.035	0.063	0.063	0.017	21	0.000	0.039	0.066	0.019	
23	-0.001	0.039	0.066	0.066	0.019	23	0.000	0.034	0.064	0.011	
25	-0.023	0.044	0.074	0.074	0.021	25	-0.005	0.052	0.080	0.027	
28	-0.027	0.047	0.075	0.075	0.022	28	-0.007	0.055	0.088	0.030	
30	-0.027	0.048	0.081	0.081	0.023	30	-0.008	0.057	0.089	0.034	
32	-0.028	0.049	0.081	0.081	0.026	32	-0.006	0.063	0.103	0.036	
35	-0.054	0.057	0.097	0.097	0.03	35	0.008	0.060	0.101	0.033	
37	0.009	0.069	0.11	0.11	0.042	37	-0.003	0.076	0.118	0.048	
39	0.01	0.073	0.115	0.115	0.045	39	-0.005	0.084	0.133	0.056	
43	0.009	0.079	0.128	0.128	0.051	43	-0.006	0.092	0.142	0.060	
44	0.009	0.085	0.136	0.136	0.054	44	-0.004	0.100	0.147	0.063	
46	0.01	0.096	0.143	0.143	0.059	46					

CONCENTRATION Day	Neg Control Conc	P1 Conc	P2 Conc	P3 Conc	Pos Control Conc	CONCENTRATION Day	P1C Conc	P2C Conc	P3C Conc	Avg (P1, P2, P3) Conc
0	0.000348743	0.00051095	0.0005109	0.0003893	0.015639418	0	0			
2	0.000308191	0.00042985	0.0005109	0.0003487	0.017664234	2	-1.62296E-05	0.00146	-0.00014	-2.7034E-06
4	0.000105434	0.0005515	0.0007137	0.0004298	0.018407948	4	0.000754258	0.001038	0.00047	0.000754258
7	0.000145985	0.00087591	0.0011598	0.0005921	0.018961882	7	0.000754258	0.001119	0.000389	0.000754258
9	0.00026764	0.00099757	0.0013625	0.0006328	0.019083538	9	0.000997567	0.001606	0.000592	0.001065153
11	0.000308191	0.0011922	0.0017275	0.0007137	0.018961882	11	0.001403082	0.002214	0.000876	0.001487702
14	6.48824E-05	0.00132198	0.002133	0.0007948	0.018759124	14	0.001443633	0.002376	0.002579	0.002133009
16	0.00026764	0.00152474	0.0024574	0.002602	0.01892133	16	0.001524738	0.00262	0.000916	0.001686942
18	0.000348743	0.00152474	0.0026198	0.0009165	0.018840227	18	0.001727494	0.002853	0.000998	0.001852666
21	0.000308191	0.00176805	0.0029035	0.0010381	0.018840227	21	0.001930251	0.003025	0.001119	0.002024872
23	0.000389294	0.00193025	0.0030251	0.001192	0.018840227	23	0.001727494	0.002944	0.000795	0.001822114
25	-0.000583942	0.00211301	0.0033496	0.0012003	0.019245742	25	0.001727494	0.002944	0.000795	0.001822114
28	-0.000746148	0.00225456	0.0033801	0.0012409	0.018633747	28	0.002457421	0.003317	0.001565	0.002587213
30	-0.000746148	0.00229521	0.0036334	0.0012814	0.018555367	30	0.002579075	0.003357	0.001444	0.002497972
32	-0.000746148	0.00233577	0.0036334	0.0014031	0.018515615	32	0.002660178	0.003358	0.001727	0.002781633
35	-0.002246553	0.00266018	0.0042822	0.0015633	0.018598918	35	0.002903487	0.004526	0.001809	0.003079211
37	0.000713706	0.00314568	0.0048034	0.0020519	0.019205191	37	0.002781633	0.004444	0.001687	0.002971073
39	0.000754258	0.003309	0.0050122	0.0021735	0.018718573	39	0.00330657	0.005134	0.002295	0.003518897
43	0.000754258	0.0035231	0.0055399	0.0024169	0.01863747	43	0.003755069	0.005742	0.00262	0.004038929
44	0.000713706	0.00363617	0.0059637	0.0025385	0.018598918	44	0.004079481	0.006107	0.002762	0.004322719
46	0.000754258	0.00424169	0.0061476	0.0027413	0.018678021	46	0.004403893	0.006531	0.002903	0.004539065

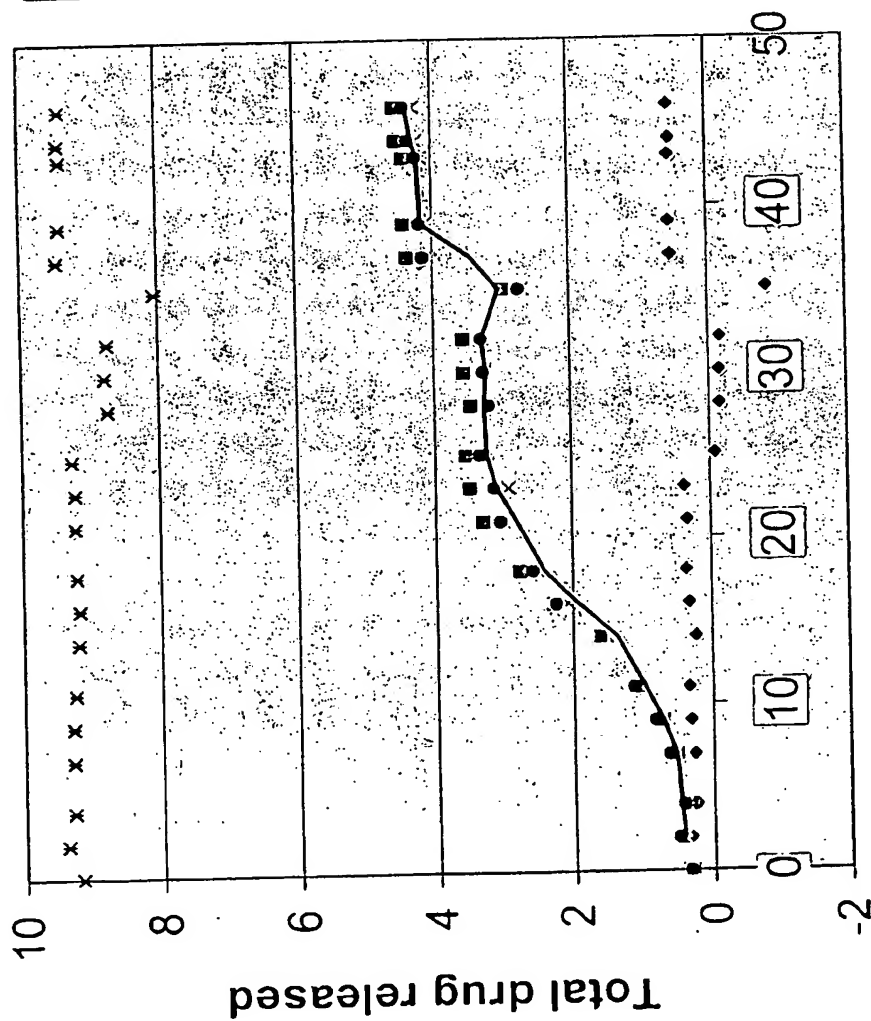
500 mL Corrected Day	Neg Control Total Drug	P1 Total Drug	P2 Total Drug	P3 Total Drug	Pos Control Total Drug	Avg (P1, P2, P3) Total Drug	500 mL Corrected Day	P1C Total Drug	P2C Total Drug	P3C Total Drug	Avg (P1, P2, P3) Total Drug
0	0.174371452	0.25547445	0.25547445	0.1946472	7.919708029	0.235198702	0	0.255474453	0.255474	0.194647	0.235198702
2	0.154095702	0.21492295	0.2554745	0.1743715	8.832116788	0.214922952	2	0.214922952	0.255474	0.174371	0.214922952
4	0.052716951	0.2757502	0.3568532	0.214923	9.703974047	0.262508786	4	-0.0081103	0.072993	-0.06894	-0.001351717
7	0.072982701	0.4379562	0.5798865	0.296026	9.480940795	0.437956204	7	0.377128954	0.519059	0.235199	0.377128954
9	0.133819951	0.49878345	0.6812652	0.3163017	9.541768045	0.498783455	9	0.377128954	0.559611	0.194647	0.377128954
11	0.154095702	0.55961071	0.863747	0.3566532	9.480940795	0.553403623	11	0.498783455	0.80292	0.296026	0.532575372
14	0.0324412	0.66098946	1.0665045	0.3974047	9.379562044	0.70829954	14	0.701540957	1.107056	0.437956	0.746851041
16	0.133819951	0.76236921	1.2287105	1.3300892	9.460665045	1.107055961	16	0.721816707	1.188159	1.289538	1.066504461
18	0.174371452	0.76236921	1.3098135	0.458232	9.420113544	0.843471208	18	0.762368208	1.309813	0.458232	0.843471208
21	0.154095702	0.88402271	1.4517437	0.5190592	9.440388204	0.951608543	21	0.863746959	1.431468	0.498783	0.931332793
23	0.194647202	0.96512571	1.512571	0.5596107	9.420113544	1.012435793	23	0.96512571	1.512571	0.559611	1.012435793
25	-0.291970803	1.06550446	1.674777	0.6001622	9.622871046	1.113815444	25	0.863746959	1.472018	0.397405	0.911057042
28	-0.373073804	1.12733171	1.6950527	0.620438	9.318734793	1.147607461	28	1.228710462	1.796431	0.721617	1.248986212
30	-0.353349554	1.16788321	1.8167072	0.6407137	9.278183293	1.201676129	30	1.289537713	1.958637	0.782844	1.34380638
32	-0.353349554	1.16788321	1.8167072	0.701541	9.257907543	1.228710462	32	1.330089213	1.978913	0.863747	1.390916464
35	-1.123276581	1.33008921	2.141182	0.782544	9.298459043	1.417950798	35	1.451743715	2.262774	0.904288	1.539605299
37	0.356653204	1.57339822	2.404704	1.025953	9.602555296	1.668018383	37	1.390916464	2.222222	0.843471	1.485536632
39	0.377128954	1.65450122	2.5060827	1.0867802	9.359286294	1.749121384	39	1.715328467	2.56691	1.147607	1.809948635
43	0.377128954	1.77615572	2.7696675	1.2084347	9.318734793	1.918085969	43	1.877534469	2.871046	1.309813	2.01946472
44	0.356653204	1.91808597	2.9318735	1.269262	9.298459043	2.03974047	44	2.03974047	3.053528	1.390916	2.161394972
46	0.377128954	2.12084347	3.0738037	1.3706407	9.339010543	2.188429305	46	2.201946472	3.154907	1.451744	2.269532396

20% 85:15 RISP



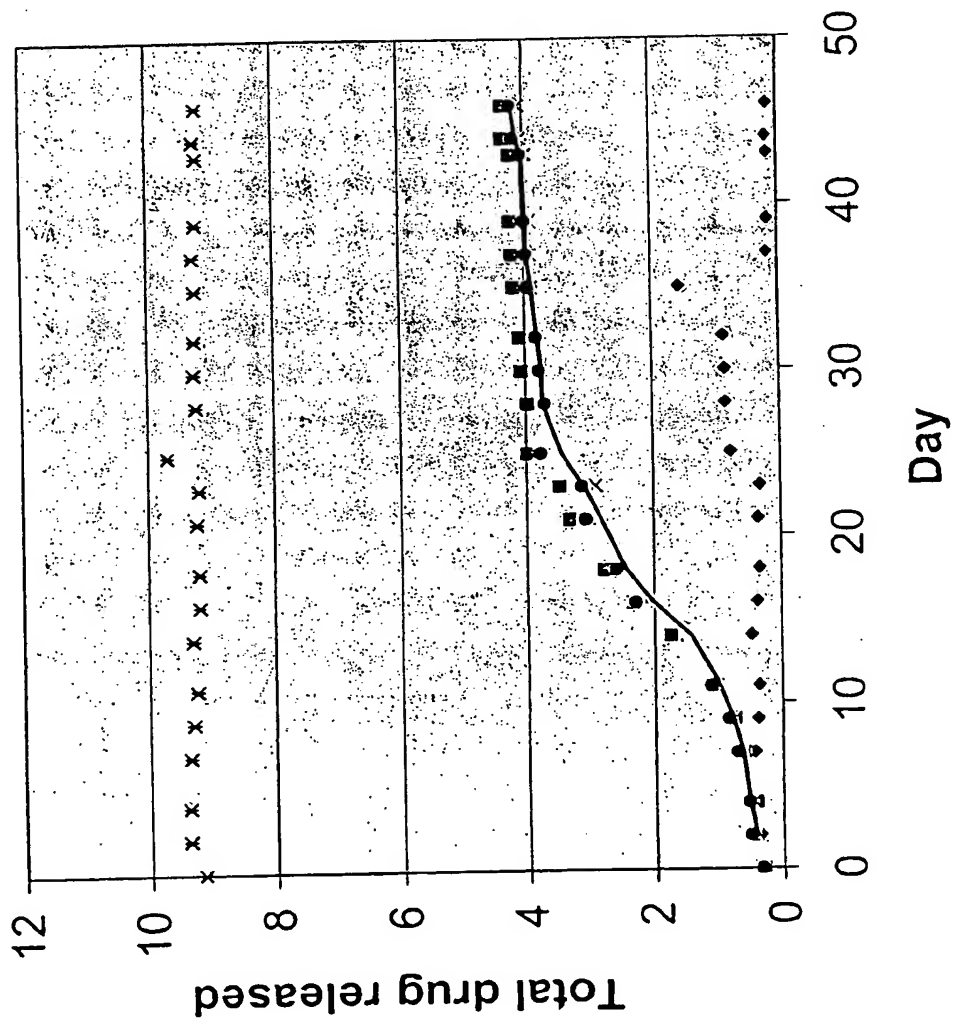
Day

20% 85:15 RISP {NEW}



Day

20% 85:15 RISP {NEG CORRECTED}



◆ Neg Control

■ P1

▲ P2

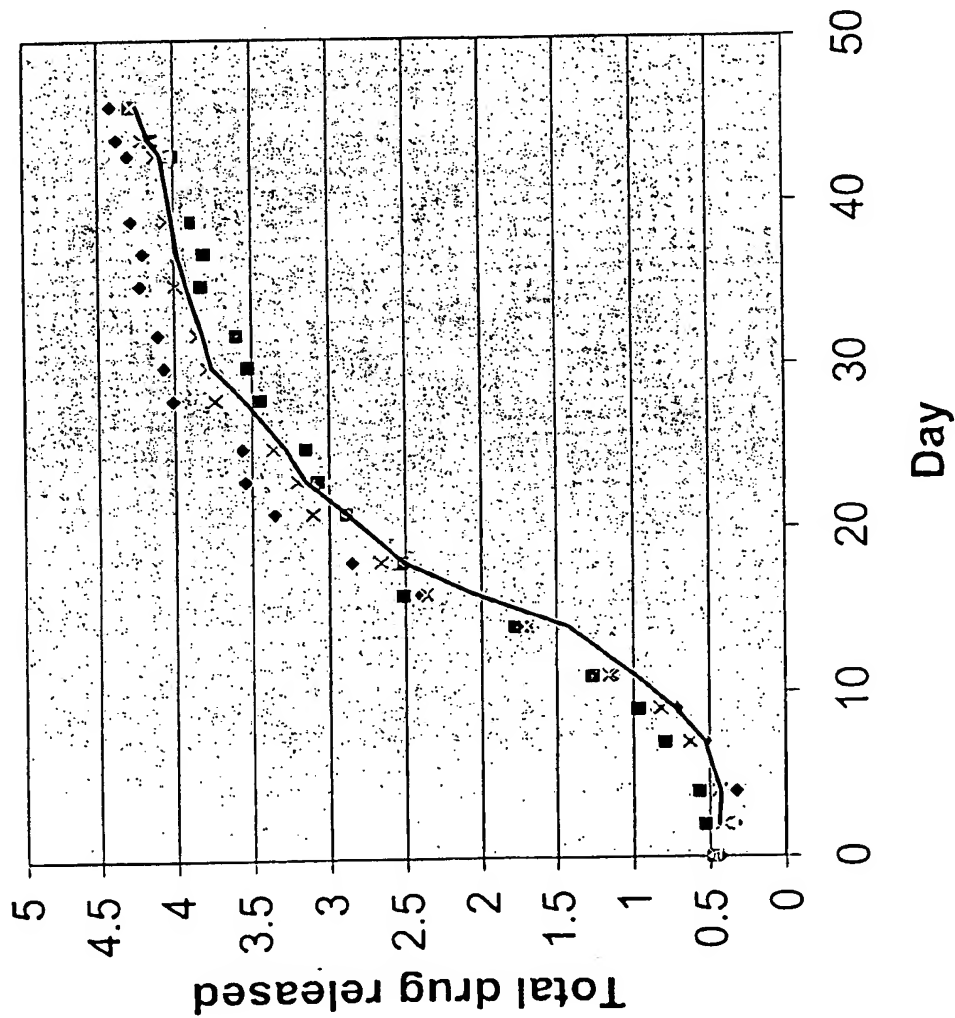
× P3

* Pos Control

● Avg (P1, P2, P3)

— 2 per. Mov. Avg. (Avg (P1, P2, P3))

20% 85:15 RISIP {POS & NEG CORRECTED}



♦ P1C

■ P2C

▲ P3C

× Avg (P1C, P2C, P3C)

— 2 per. Mov. Avg. (Avg (P1C, P2C, P3C))

20% RISP 85:15

ABSORBANCE Day	Neg Control ABS	P1 ABS	P2 ABS	P3 ABS	Pos Control ABS	20% RISP 85:15	new	ABSORBANCE Day	Neg Control ABS	P1 ABS	P2 ABS	P3 ABS	Pos Control ABS	20% RISP 85:15		ABSORBANCE Day	Neg Control ABS	P1 ABS	P2 ABS	P3 ABS	Pos Control ABS		
														0	0.468								
0	0	0	-0.002	0	0	0		0	0	0	-0.002	0	0	0	0	0	0	0	-0.002	0	0	0	0.468
2	-0.001	0.004	0.014	0.005	0.005	0.479		2	-0.001	0.004	0.014	0.005	0.005	0.479	2	-0.001	0.004	0.014	0.005	0.005	0.005	0.005	0.479
4	-0.006	-0.002	0.011	0.003	0.003	0.474		4	-0.006	-0.002	0.011	0.003	0.003	0.474	4	-0.006	-0.002	0.011	0.003	0.003	0.003	0.003	0.474
7	-0.005	0.009	0.023	0.011	0.011	0.474		7	-0.005	0.009	0.023	0.011	0.011	0.474	7	-0.005	0.009	0.023	0.011	0.011	0.011	0.011	0.474
9	-0.002	0.019	0.032	0.022	0.022	0.474		9	-0.002	0.019	0.032	0.022	0.022	0.474	9	-0.002	0.019	0.032	0.022	0.022	0.022	0.022	0.474
11	-0.001	0.038	0.046	0.035	0.035	0.472		11	-0.001	0.038	0.046	0.035	0.035	0.472	11	-0.001	0.038	0.046	0.035	0.035	0.035	0.035	0.472
14	-0.007	0.066	0.07	0.062	0.062	0.469		14	-0.007	0.066	0.07	0.062	0.062	0.469	14	-0.007	0.066	0.07	0.062	0.062	0.062	0.062	0.469
16	-0.002	-0.102	0.108	0.091	0.091	0.468		16	-0.002	-0.102	0.108	0.091	0.091	0.468	16	-0.002	-0.102	0.108	0.091	0.091	0.091	0.091	0.468
18	0	0.128	0.111	0.115	0.115	0.47		18	0	0.128	0.111	0.115	0.115	0.47	18	0	0.128	0.111	0.115	0.115	0.115	0.115	0.47
21	-0.001	0.156	0.131	0.141	0.141	0.471		21	-0.001	0.156	0.131	0.141	0.141	0.471	21	-0.001	0.156	0.131	0.141	0.141	0.141	0.141	0.471
23	0.001	0.166	0.141	0.159	0.159	0.471		23	0.001	0.166	0.141	0.159	0.159	0.471	23	0.001	0.166	0.141	0.159	0.159	0.159	0.159	0.471
25	-0.023	0.169	0.147	0.159	0.159	0.473		25	-0.023	0.169	0.147	0.159	0.159	0.473	25	-0.023	0.169	0.147	0.159	0.159	0.159	0.159	0.473
28	-0.027	0.165	0.135	0.151	0.151	0.445		28	-0.027	0.165	0.135	0.151	0.151	0.445	28	-0.027	0.165	0.135	0.151	0.151	0.151	0.151	0.445
30	-0.027	0.17	0.141	0.154	0.154	0.447		30	-0.027	0.17	0.141	0.154	0.154	0.447	30	-0.027	0.17	0.141	0.154	0.154	0.154	0.154	0.447
32	-0.028	0.17	0.143	0.156	0.156	0.445		32	-0.028	0.17	0.143	0.156	0.156	0.445	32	-0.028	0.17	0.143	0.156	0.156	0.156	0.156	0.445
35	-0.064	0.139	0.118	0.124	0.124	0.408		35	-0.064	0.139	0.118	0.124	0.124	0.408	35	-0.064	0.139	0.118	0.124	0.124	0.124	0.124	0.408
37	0.009	0.213	0.192	0.199	0.199	0.483		37	0.009	0.213	0.192	0.199	0.199	0.483	37	0.009	0.213	0.192	0.199	0.199	0.199	0.199	0.483
39	0.01	0.215	0.195	0.199	0.199	0.481		39	0.01	0.215	0.195	0.199	0.199	0.481	39	0.01	0.215	0.195	0.199	0.199	0.199	0.199	0.481
43	0.01	0.215	0.2	0.202	0.202	0.48		43	0.01	0.215	0.2	0.202	0.202	0.48	43	0.01	0.215	0.2	0.202	0.202	0.202	0.202	0.48
44	0.009	0.22	0.208	0.205	0.205	0.481		44	0.009	0.22	0.208	0.205	0.205	0.481	44	0.009	0.22	0.208	0.205	0.205	0.205	0.205	0.481
46	0.01	0.221	0.214	0.207	0.207	0.48		46	0.01	0.221	0.214	0.207	0.207	0.48	46	0.01	0.221	0.214	0.207	0.207	0.207	0.207	0.48

CONCENTRATION Day	Neg Control Conc	P1		P2		P3		Pos Control		mg/ml
		Conc	Avg (P1, P2, P3)	Conc	Avg (P1, P2, P3)	Conc	Avg (P1, P2, P3)	Conc	Avg (P1, P2, P3)	
0	0.000715793	0.00064045	0.0007158	0.0007158	0.018346896	0.000630677	0.000716	0.000716	0.018347	0.000691
2	0.000678119	0.00066649	0.0012432	0.0009042	0.018761302	0.001004621	0.000866	0.001243	0.000904	0.018761
4	0.000469753	0.00064045	0.0011302	0.0008268	0.018572936	0.000866486	0.000866	0.00113	0.000829	0.018573
7	0.000527426	0.00105465	0.0015923	0.0011302	0.018572936	0.001255777	0.001582	0.001055	0.001582	0.018573
9	0.000640446	0.00143159	0.0019213	0.0015446	0.018572936	0.00163251	0.001921	0.001432	0.001921	0.018573
11	0.000678119	0.00214738	0.0024688	0.002072	0.018497569	0.002227275	0.002469	0.002147	0.002469	0.018498
14	0.00045208	0.00320223	0.0033529	0.0030515	0.018346896	0.00449568	0.003353	0.003202	0.003353	0.018347
16	0.000640446	0.00455947	0.0047845	0.0041441	0.018346896	0.00690516	0.004558	0.004559	0.004144	0.004496
18	0.000715793	0.00553787	0.0046975	0.0050482	0.018422242	0.005181242	0.004698	0.005538	0.005048	0.018422
21	0.000678119	0.00539283	0.005651	0.0060277	0.018459916	0.006555154	0.005593	0.005393	0.006028	0.01846
23	0.000753465	0.00569356	0.0060277	0.0059762	0.018459916	0.006555154	0.006028	0.006028	0.005979	0.01846
25	-0.000150693	0.00708258	0.0062538	0.006017	0.018535262	0.006660731	0.006254	0.007083	0.006254	0.018535
28	-0.000301388	0.00693169	0.0068017	0.006045	0.01748041	0.006379345	0.006802	0.006932	0.006045	0.01748
30	-0.000301388	0.00712025	0.0060277	0.006175	0.017555756	0.006555154	0.006028	0.00712	0.006175	0.017556
32	-0.00033906	0.00712025	0.0061031	0.0065928	0.01748041	0.006555154	0.006103	0.00712	0.006593	0.01748
35	-0.001695298	0.00595238	0.0051612	0.0053873	0.016286498	0.005500301	0.005161	0.005952	0.005387	0.016286
37	0.001954852	0.0087402	0.0079491	0.0081751	0.018911995	0.008288125	0.007949	0.00874	0.008175	0.018912
39	0.001092526	0.00881555	0.0082128	0.0082128	0.018836649	0.008463934	0.008213	0.008816	0.008213	0.018837
43	0.001092526	0.00881555	0.0082128	0.0082128	0.018836649	0.008463934	0.008213	0.008816	0.008213	0.018837
44	0.001054852	0.00590372	0.0055518	0.0084388	0.018836649	0.008664858	0.005552	0.009004	0.008439	0.018837
46	0.001092526	0.005904159	0.0087778	0.0085142	0.018798975	0.00877778	0.008778	0.009042	0.008514	0.018799

corrected for negative control									
Day	neg control	P1	correct	P2	correct	P3	correct	Pos control	Pos corrected
0	0	0	-0.002	0	0	0	0	0.468	0.468
2	0.001	0.005	0.015	0.006	0.006	0.006	0.006	0.46	0.46
4	0.006	0.004	0.017	0.009	0.009	0.009	0.009	0.46	0.46
7	0.005	0.014	0.028	0.016	0.016	0.016	0.016	0.479	0.479
9	0.002	0.021	0.034	0.024	0.024	0.024	0.024	0.476	0.476
11	0.001	0.039	0.047	0.037	0.037	0.037	0.037	0.473	0.473
14	0.007	0.073	0.077	0.069	0.069	0.069	0.069	0.476	0.476
16	0.002	0.104	0.111	0.093	0.093	0.093	0.093	0.47	0.47
18	0	0.128	0.131	0.115	0.115	0.115	0.115	0.47	0.47
21	0.001	0.157	0.132	0.142	0.142	0.142	0.142	0.472	0.472
23	-0.001	0.165	0.14	0.135	0.135	0.135	0.135	0.47	0.47
25	0.023	0.192	0.17	0.162	0.162	0.162	0.162	0.496	0.496
28	0.027	0.197	0.168	0.161	0.161	0.161	0.161	0.474	0.474
30	0.027	0.197	0.168	0.161	0.161	0.161	0.161	0.474	0.474
32	0.028	0.198	0.171	0.164	0.164	0.164	0.164	0.473	0.473
35	0.064	0.203	0.182	0.166	0.166	0.166	0.166	0.472	0.472
37	-0.009	0.204	0.183	0.169	0.169	0.169	0.169	0.474	0.474
39	-0.01	0.205	0.185	0.169	0.169	0.169	0.169	0.471	0.471
43	-0.01	0.205	0.19	0.192	0.192	0.192	0.192	0.47	0.47
44	-0.009	0.211	0.199	0.196	0.196	0.196	0.196	0.472	0.472
46	-0.01	0.211	0.204	0.197	0.197	0.197	0.197	0.47	0.47
								0.47419	0.47419

Corrected for Negative and Positive Control									
Day	Positive Correction Coefficient				P1C	P2C	P3C		
0	-0.00619	0.00419	0.00619	0.00619	0.00619	0.00619	0.00619	0.00619	0.00619
2	0.00581	-0.0081	0.00919	0.00919	0.00919	0.00919	0.00919	0.00919	0.00919
4	0.00581	-0.0081	0.01119	0.01119	0.01119	0.01119	0.01119	0.01119	0.01119
7	0.00481	0.00919	0.02319	0.02319	0.02319	0.02319	0.02319	0.02319	0.02319
9	0.00181	0.01919	0.03219	0.03219	0.03219	0.03219	0.03219	0.03219	0.03219
11	-0.00119	0.04019	0.04819	0.04819	0.04819	0.04819	0.04819	0.04819	0.04819
14	0.00181	0.07119	0.07519	0.07519	0.07519	0.07519	0.07519	0.07519	0.07519
16	-0.00419	0.10819	0.11419	0.11419	0.11419	0.11419	0.11419	0.11419	0.11419
18	-0.00419	0.13219	0.11519	0.11519	0.11519	0.11519	0.11519	0.11519	0.11519
21	-0.00219	0.15919	0.13419	0.13419	0.13419	0.13419	0.13419	0.13419	0.13419
23	-0.00419	0.16919	0.14419	0.14419	0.14419	0.14419	0.14419	0.14419	0.14419
25	0.02181	0.17019	0.14819	0.14819	0.14819	0.14819	0.14819	0.14819	0.14819
28	-0.00219	0.19419	0.16419	0.16419	0.16419	0.16419	0.16419	0.16419	0.16419
30	-0.00019	0.19719	0.16819	0.16819	0.16819	0.16819	0.16819	0.16819	0.16819
32	-0.00119	0.19919	0.17219	0.17219	0.17219	0.17219	0.17219	0.17219	0.17219
35	-0.00219	0.20519	0.18419	0.18419	0.18419	0.18419	0.18419	0.18419	0.18419
37	-0.00019	0.20419	0.18319	0.18319	0.18319	0.18319	0.18319	0.18319	0.18319
39	-0.00319	0.20819	0.18819	0.18819	0.18819	0.18819	0.18819	0.18819	0.18819
43	-0.00419	0.20919	0.19419	0.19419	0.19419	0.19419	0.19419	0.19419	0.19419
44	-0.00219	0.21319	0.20119	0.20119	0.20119	0.20119	0.20119	0.20119	0.20119
46	-0.00419	0.21519	0.20819	0.20819	0.20819	0.20819	0.20819	0.20819	0.20819

CONCENTRATION									
Day	CONCENT	Neg	Contr	P1	P2	P3	Pos Control	Avg (P1, P2, P3)	
0	0.000716	0.00064	0.00716	0.00716	0.00716	0.00716	0.018247	0.006991	0.006991
2	0.000753	0.00594	0.01281	0.00594	0.018799	0.018799	0.01042	0.001042	0.001042
4	0.000942	0.00866	0.01356	0.001055	0.018799	0.018799	0.01042	0.001042	0.001042
7	0.000904	0.01243	0.001771	0.001319	0.018761	0.018761	0.01444	0.001444	0.001444
9	0.000781	0.01507	0.001997	0.00162	0.018848	0.018848	0.01708	0.001708	0.001708
11	0.000753	0.02185	0.002486	0.00211	0.018535	0.018535	0.00226	0.00226	0.00226
14	0.00098	0.003468	0.003617	0.003315	0.018648	0.018648	0.003466	0.003466	0.003466
16	0.000781	0.004534	0.004466	0.004219	0.018422	0.018422	0.004571	0.004571	0.004571
18	0.000716	0.005538	0.004899	0.005048	0.018422	0.018422	0.005101	0.005101	0.005101
21	0.000753	0.006631	0.005689	0.005065	0.018498	0.018498	0.006128	0.006128	0.006128
23	0.000678	0.006332	0.00559	0.005602	0.018422	0.018422	0.006241	0.006241	0.006241
25	0.001582	0.007949	0.00712	0.007572	0.018402	0.018402	0.007547	0.007547	0.007547
28	0.00133	0.007949	0.006819	0.007422	0.018498	0.018498	0.007397	0.007397	0.007397
30	0.001733	0.008137	0.007045	0.007535	0.018573	0.018573	0.007572	0.007572	0.007572
32	0.001771	0.008175	0.007158	0.007648	0.018535	0.018535	0.00766	0.00766	0.00766
35	0.003127	0.008363	0.007572	0.007798	0.018498	0.018498	0.007911	0.007911	0.007911
37	0.00037	0.008401	0.00761	0.007836	0.018573	0.018573	0.007949	0.007949	0.007949
39	0.000339	0.008439	0.007685	0.007836	0.01846	0.01846	0.007987	0.007987	0.007987
43	0.000339	0.008439	0.007874	0.007949	0.018422	0.018422	0.008087	0.008087	0.008087
44	0.00037	0.008655	0.008213	0.0081	0.018498	0.018498	0.008326	0.008326	0.008326
46	0.000339	0.008655	0.008401	0.008137	0.018422	0.018422	0.008401	0.008401	0.008401

CONCENTRATION									
Day	P1C	P2C	P3C	Avg (P1C, P2C, P3C)					
0	0	0.000873544	0.000949	0.000949	0.000923875	0.000923875	0.000923875	0.000923875	0.000923875
2	2	0.000685277	0.001062	0.000723	0.000823413	0.000823413	0.000823413	0.000823413	0.000823413
4	4	0.000647604	0.001137	0.000836	0.000873644	0.000873644	0.000873644	0.000873644	0.000873644
7	7	0.00106201	0.001589	0.001137	0.001262934	0.001262934	0.001262934	0.001262934	0.001262934
9	9	0.001438743	0.001928	0.001552	0.001639567	0.001639567	0.001639567	0.001639567	0.001639567
11	11	0.002229882	0.002531	0.002155	0.002305229	0.002305229	0.002305229	0.002305229	0.002305229
14	14	0.003397755	0.003548	0.003247	0.003397755	0.003397755	0.003397755	0.003397755	0.003397755
16	16	0.004791667	0.005018	0.004377	0.004728878	0.004728878	0.004728878	0.004728878	0.004728878
18	18	0.005695826	0.005955	0.005206	0.005318093	0.005318093	0.005318093	0.005318093	0.005318093
21	21	0.006713005	0.007771	0.006148	0.006210694	0.006210694	0.006210694	0.006210694	0.006210694
23	23	0.007089738	0.008148	0.006596	0.006525563	0.006525563	0.006525563	0.006525563	0.006525563
25	25	0.007127411	0.008299	0.006751	0.006755961	0.006755961	0.006755961	0.006755961	0.006755961
28	28	0.00803157	0.00901	0.007504	0.007479029	0.007479029	0.007479029	0.007479029	0.007479029
30	30	0.00814459	0.00902	0.007542	0.00753968	0.00753968	0.00753968	0.00753968	0.00753968
32	32	0.008219537	0.009203	0.007693	0.007693087	0.007693087	0.007693087	0.007693087	0.007693087
35	35	0.008445976	0.009555	0.007881	0.007956224	0.007956224	0.007956224	0.007956224	0.007956224
37	37	0.008408303	0.009761	0.007843	0.007956224	0.007956224	0.007956224	0.007956224	0.007956224
39	39	0.008558996	0.009806	0.007956	0.008024502	0.008024502	0.008024502	0.008024502	0.008024502
43	43	0.00859667	0.009802	0.008107	0.008107	0.008107	0.008107	0.008107	0.008107
44	44	0.008747353	0.009235	0.008182	0.008182	0.008182	0.008182	0.008182	0.008182
46	46	0.008822709	0.009559	0.008295	0.008295	0.008295	0.008295	0.008295	0.008295

500 mL Corrected Day	Total Drug Neg Control	Total Drug P1	Total Drug P2	Total Drug P3	Total Drug Pos Control	Total Drug Avg (P1, P2, P3)	Total Drug in milligrams
0	0.357896	0.320230	0.357896	0.357896	9.173448	0.345336	557
2	0.33906	0.433243	0.621609	0.45208	9.386531	0.502311	10629
4	0.244876	0.320230	0.565099	0.414406	9.286467	0.433243	2517
7	0.263713	0.527426	0.781139	0.565099	9.286468	0.627888	266
9	0.320230	0.715793	0.960669	0.772303	9.286468	0.816255	4772
11	0.33906	1.073689	1.224382	1.036016	9.248794	1.111362	266
14	0.22604	1.601115	1.676462	1.525769	8.192285	1.601115	1513
16	0.320230	2.279234	2.392254	2.072031	8.173448	2.24784	4064
18	0.357896	2.768987	2.448764	2.524111	9.211121	2.580621	1157
21	0.33906	3.296414	2.825497	3.013864	9.229558	3.045258	188
23	0.376733	3.48478	3.013864	2.916881	9.229558	3.19441	333
25	-0.07535	3.54129	3.126884	3.52923	9.287631	3.340366	562
28	-0.15069	3.65943	2.900844	3.20223	8.740205	3.18872	493
30	-0.16953	3.560127	3.051537	3.296414	8.740205	3.302892	385
32	-0.84765	2.97619	2.590621	2.693641	8.043249	2.750151	8945
35	0.527426	4.370102	3.974539	4.06753	9.45598	4.144063	2688
37	0.546263	4.407776	4.031043	4.106388	9.418324	4.181736	7048
39	0.546263	4.407776	4.125226	4.162899	9.39948	4.231967	44
44	0.527426	4.501959	4.275918	4.219409	9.418324	4.332429	174
46	0.546263	4.520796	4.388939	4.257083	9.39948	4.388939	12

500 mL Corrected Day	Total Drug Neg Control	Total Drug P1	Total Drug P2	Total Drug P3	Total Drug Pos Control	Total Drug Avg (P1, P2, P3)	Total Drug in milligrams
0	0.357896	0.320230	0.357896	0.357896	9.173448	0.345336	557
2	0.33906	0.433243	0.621609	0.45208	9.386531	0.502311	10629
4	0.244876	0.320230	0.565099	0.414406	9.286467	0.433243	2517
7	0.263713	0.527426	0.781139	0.565099	9.286468	0.627888	266
9	0.320230	0.715793	0.960669	0.772303	9.286468	0.816255	4772
11	0.33906	1.073689	1.224382	1.036016	9.248794	1.111362	266
14	0.22604	1.601115	1.676462	1.525769	8.192285	1.601115	1513
16	0.320230	2.279234	2.392254	2.072031	8.173448	2.24784	4064
18	0.357896	2.768987	2.448764	2.524111	9.211121	2.580621	1157
21	0.33906	3.296414	2.825497	3.013864	9.229558	3.045258	188
23	0.376733	3.48478	3.013864	2.916881	9.229558	3.19441	333
25	-0.07535	3.54129	3.126884	3.52923	9.287631	3.340366	562
28	-0.15069	3.65943	2.900844	3.20223	8.740205	3.18872	493
30	-0.16953	3.560127	3.051537	3.296414	8.740205	3.302892	385
32	-0.84765	2.97619	2.590621	2.693641	8.043249	2.750151	8945
35	0.527426	4.370102	3.974539	4.06753	9.45598	4.144063	2688
37	0.546263	4.407776	4.031043	4.106388	9.418324	4.181736	7048
39	0.546263	4.407776	4.125226	4.162899	9.39948	4.231967	44
44	0.527426	4.501959	4.275918	4.219409	9.418324	4.332429	174
46	0.546263	4.520796	4.388939	4.257083	9.39948	4.388939	12

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